SCIENTIFIC INVESTIGATIONS

Relationships Between Sleep Quality and pH Monitoring Findings in Persons with Gastroesophageal Reflux Disease

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Background: Nighttime reflux has been shown to be associated with esophageal mucosal injury, complications, and extra-esophageal manifestations. However, few studies have assessed the impact of gastroesophageal reflux on reported quality of sleep and quality of sleep on gastroesophageal reflux.

Aims: The aims of this study were (1) to determine the correlation between the severity of gastroesophageal reflux disease (GERD) symptoms and esophageal acid contact time and subjects' perceived quality of sleep; (2) to investigate the correlation between reported quality of sleep of the night prior and severity of GERD symptoms and esophageal acid contact time the following day; and (3) to define in a sleep laboratory the correlation between acid reflux events and sleep architecture.

Methods: Subjects with typical GERD symptoms ≥3 times a week underwent upper endoscopy and pH monitoring. These subjects subsequently completed the GERD Symptom Assessment Score (GSAS), and the Sleep Heart Health Study Sleep Habits (SHHS) Questionnaire to assess baseline sleep symptoms and GERD symptoms, including an index of GERD symptom severity (GERD symptom index). Before and after the pH test, the patients completed a different instrument, the Sleep Quality Questionnaire, utilized specifically to assess the quality of each subject's sleep before and after pH testing. Fifteen randomly selected subjects also underwent a polysomnographic study during the pH test.

Results: Forty-eight (33 males/15 females, mean age 48.8 ± 17.1 y) subjects were prospectively recruited. Using data from the GSAS and SHHS questionnaires, disorders of initiating and maintaining sleep were found to be positively associated with greater severity of the GERD symptom index (r = 0.33, p <0.05). More frequent awakenings also correlated with a higher GERD symptom index (r = 0.4, p <0.01). Correlations between the Sleep Quality Questionnaire on the night before sleep testing and pH monitoring data showed that subjects with poorer sleep quality had longer acid reflux events (r=-0.34, p<0.05). More perceived awakenings also were correlated with the number of supine acid reflux events > 5 min (r=0.31, p<0.05) and the duration of the longest supine acid reflux event (r = 0.28, p = 0.05). Inverse correlations were observed between overall sleep quality on the pH testing night and a higher percentage of time spent with pH<4 supine (r=-0.432, p <0.002), and the duration of the longest acid reflux event during the entire night (r = -0.38, p <0.01) and supine (r=-0.37, p<0.02).

Conclusions: Persons with worse GERD symptoms report poorer subject sleep quality. Poor sleep quality on the night prior to pH testing was associated with more acid exposure the following day. Greater acid exposure at night was related to a worse perception of sleep quality the next day. These findings suggest important interactions between GERD and sleep quality.

Keywords: GERD, sleep, pH test, heartburn

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is very common, affecting up to 44% of the adult U.S. population monthly

and 20% weekly. Classic GERD symptoms include heartburn and acid regurgitation; these symptoms are common during the day and may also awaken subjects from sleep during the night. Nocturnal GERD symptoms have been shown to affect quality of sleep and subsequent daytime function. Quality of sleep in persons with GERD may also be affected by acid reflux-related short arousals, for which the person is commonly amnestic, but these arousals lead to sleep fragmentation.

Heartburn that awakens patients during sleep affects approximately 25% of the general U.S. population >40 years of age. A recent national survey in subjects with heartburn symptoms demonstrated that 79% of the respondents reported having symptoms at night. Of those, 63% reported that their symptoms affected their ability to get a good night's sleep, 75% reported that symptoms kept them from falling asleep or woke them up during sleep, and 40% indicated that heartburn had some effect on their ability to function well at work the next day. Daytime reflux events tend to be more frequent and of shorter duration than those during sleep.

Reflux events during sleep differ from those during the day as the result of physiological changes that occur with the onset of sleep. These physiological changes include marked decline in the frequency of swallowing events resulting in reduced primary peristalsis and consequently in reduced delivery of saliva to the distal portion of the esophagus, loss of gravitational drainage, slower gastric emptying, and diminished conscious perception of gastroesophageal reflux events. These sleep related changes may lead to delayed esophageal acid clearance and as a result, increased acid-mucosal contact time. Thus, there is considerable evidence to indicate that GERD can affect normal sleep physiology, and cause sleep disturbances and poor quality of sleep. Conversely, it is also possible that disturbed sleep enhances perception of intra-esophageal reflux events, perhaps through centrally-mediated mechanisms. However, evidence supporting such a hypothesis is lacking.

To investigate whether GERD disturbs sleep and whether poor sleep increases GERD severity, we performed this study with the following aims: 1) to determine the correlation between GERD symptom severity and esophageal acid contact time on subsequent perception of sleep quality; 2) to determine in persons with GERD the correlation between sleep quality and reported severity of GERD symptoms and esophageal acid reflux events the next day; and 3) to assess in a sleep laboratory the correlation between sleep architecture, and acid reflux and autonomic parameters of persons with GERD.

MATERIALS AND METHODS

Subjects

Potential subjects reporting symptoms of GERD were recruited from the primary care and gastroenterology clinics of the University of Arizona Health Sciences Center and the Southern Arizona Veterans Affairs Health Care System. These symptoms included heartburn and/or acid regurgitation ≥3 times a week. Individuals receiving anti-reflux medications were excluded from the study unless they were willing to discontinue proton pump inhibitor (PPI) or H_2 receptor antagonist (H_2RA) therapy, one month and two weeks, respectively, prior to enrollment. Other exclusion criteria included use of drugs such as psychotropics, narcotics, or benzodiazepines, which might affect sleep architecture or subjective sleep quality; known psychological disorders such as depression and anxiety, and other medical comorbidities that might interfere with sleep quality such as asthma, chronic obstructive lung disease, renal failure and heart failure; sleep apnea documented by history, study questionnaire (see below) or polysomnography; and a history of upper gut surgery or known malignancy. Unwillingness to sign the informed consent form or inability to complete all stages of the study also served as exclusion criteria.

Study Protocol

A total of 48 subjects were enrolled. All underwent an upper endoscopy. The purpose of the upper endoscopy was to exclude subjects who demonstrated structural abnormalities in the esophagus (other than erosive esophagitis or Barrett's esophagus), stomach, or duodenum, and to allow careful examination of the distal portion of the esophagus in order to determine the presence and extent of mucosal inflammation. Seven days later, all subjects underwent ambulatory 24-hour esophageal pH monitoring to determine the extent of distal esophageal acid exposure, number of acid reflux events, number of reflux events longer than 5 minutes, and symptom index (SI). Thereafter, subjects were administered 3 self-report questionnaires: a demographic questionnaire, the GERD Symptom Assessment Score (GSAS), and the Sleep Heart Health Study Sleep Habits Questionnaire. An additional instrument, the Sleep Quality Questionnaire, was administered prior and after subjects underwent 24-hour esophageal pH monitoring (the morning of the test and the morning of the probe removal).

Fifteen participants were randomly selected to undergo polysomnography during esophageal pH monitoring. Randomization was achieved by using a computer program that generated a sequence of random numbers. Immediately after removal of the pH probe, all participants completed the Sleep Quality Questionnaire again. Figure 1 summarizes the study design.

Upper Endoscopy

After an overnight fast, subjects were placed in the left lateral decubitus position and sedation was achieved with a combination of midazolam (Roche, Nutley, New Jersey, USA) and meperidine (Sanofi Winthrop, New York, USA). The endoscope (Olympus GIF 140) was inserted via the mouth and into the esophagus. Careful examination of the distal esophagus was performed to determine the presence of mucosal injury.

The extent of esophageal mucosal damage was assessed using the Los Angeles Classification. The distal portion of the esophagus was carefully evaluated to determine the presence of Barrett's esophagus (endoscopically seen as red color and velvet-like texture extending into the esophagus). If Barrett's esophagus was suspected, 4 quadrant biopsies were obtained every 2 cm. Barrett's esophagus was defined as the presence of intestinal metaplasia on biopsy.

Subjects with erosive esophagitis or Barrett's esophagus were classified as having GERD, and subjects who lacked any evidence of esophageal mucosal injury were considered as having non-erosive reflux disease (NERD). Categorical variables were created using the grade of erosive esophagitis, metaplasia, and dysplasia.

Ambulatory 24-Hour Esophageal pH Monitoring

After an overnight fast, a pH probe with lower esophageal sphincter identifier (Digitrapper MK III, Medtronic, Minneapolis, MN) was inserted via the nose and into the stomach. The lower esophageal sphincter identification manometry assembly is a simple system of water-perfused manometry using a combined pH and water perfused pressure catheter. The pressure lumen is located 5 cm above the distal pH sensor. By using the station pull-through technique (0.5 cm increments), identification of the proximal margin of the lower esophageal sphincter was achieved. The pH sensor was placed 5 cm above the upper margin of the lower esophageal sphincter. The pH probe was connected to a digital portable recorder. A reference electrode was attached to the subject's upper chest. Subjects were instructed to keep a diary and to record meal times, position changes, and the time and type of symptoms, while continuing everyday activities and usual diet. By using a data-logger with event buttons (markers), subjects documented the exact time of body position (upright versus supine) and of the GERD symptoms they experienced. The type
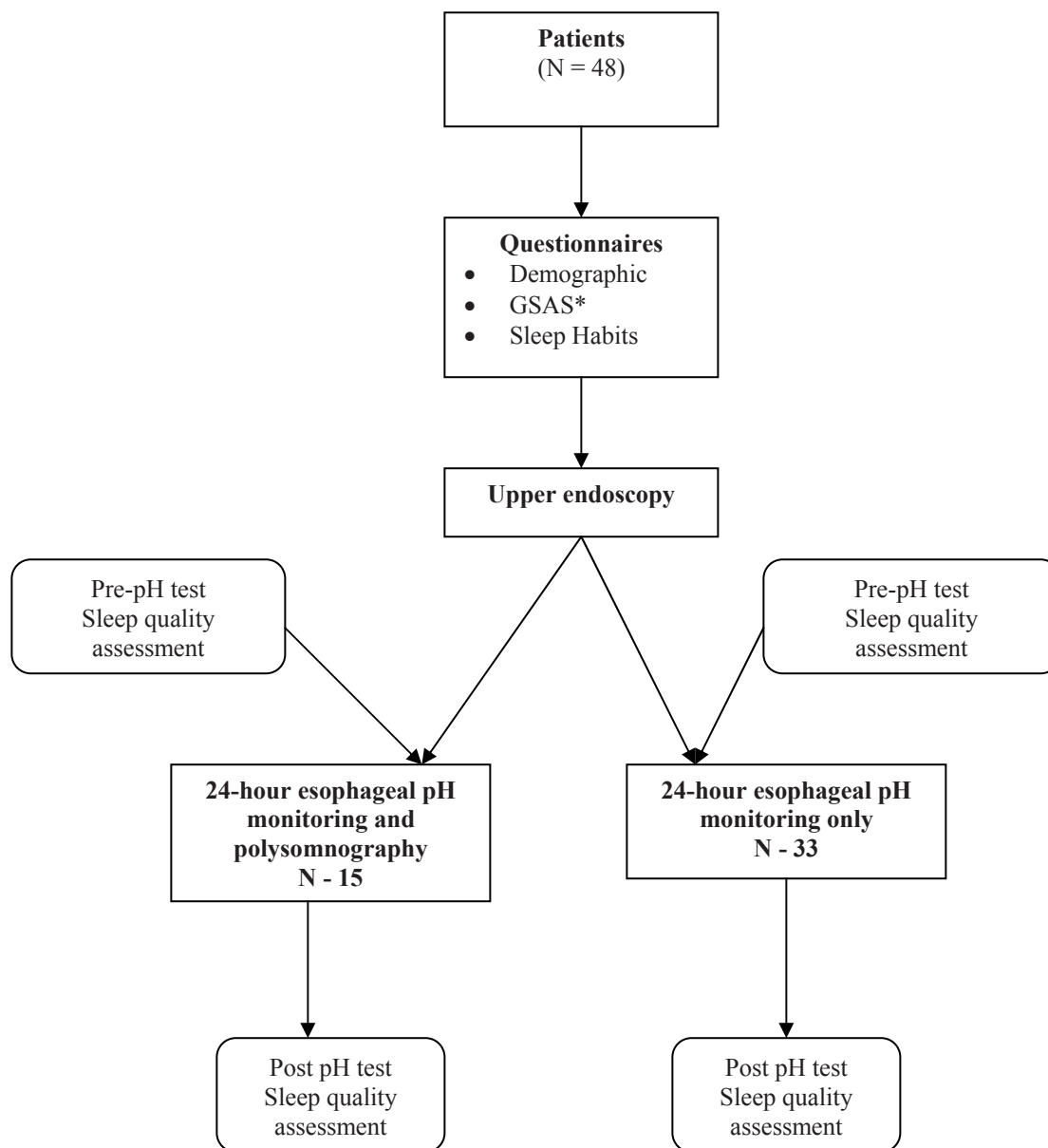
*GERD Symptom Assessment Score

Figure 1—Flow sheet of the study design

of GERD symptoms was also recorded by the subjects in the pH test diary. At the beginning and end of the study, the electrode and system were calibrated in standard solution of pH 1 and 7. Reflux was defined as a pH <4; reflux time was defined as the interval until pH was again greater than 4. The test was considered positive when the total percent time pH <4 was greater than 4.2%. The percentage time pH <4 in the supine and upright positions were considered abnormal if values were greater than 1.2% and 6%, respectively. Variables extracted from the pH report included: percent total time pH <4; percent supine time pH <4; percent upright time pH <4; total number of acid reflux events; number of acid reflux events while supine, number of acid reflux events while upright; total number of acid reflux events >5 minutes (while supine and upright); and longest acid reflux event during the pH test (while supine and upright). The symptom index (SI) was calculated as the percentage of reflux symptoms that occurred 5 minutes after an acid reflux event (pH <4). The SI was considered positive if it was equal to or greater than 50%.

$$SI\ (\%) = \frac{\text{The number of reflux symptoms episodes at pH} <4 \times 100}{\text{Total number of reflux symptoms episodes}}$$

Study Questionnaires

DEMOGRAPHIC QUESTIONNAIRE

A demographic questionnaire assessed participants' personal characteristics,such as sex, age, ethnicity, body mass index, and education level.

GERD SYMPTOM ASSESSMENT SCORE (GSAS)

The GSAS includes 15 questions that measure frequency and severity of typical (e.g., heartburn and acid regurgitation) and atypical (e.g. chest pain) GERD symptoms during the past week. This questionnaire is a validated instrument that has been used frequently to assess symptoms in GERD clinical research. Subjects were required to report if they had the symptom during the

Table 1—Summary of Patient Demographics, Frequency and Severity of Heartburn and Acid Regurgitation (GSAS and SHHS Sleep Habits Questionnaire) (n = 48)

Variable	Mean	SD	Range
Age (years)	48.8	17.1	20-82
Body mass index (kg/m²)	28.5	4.5	20.4-39.2
Frequency of heartburn (past week)	7.2	9.0	3-42
Severity of heartburn (past week)	1.4	0.9	0-3
Frequency of acid regurgitation (past week)	2.2	5.4	0-35
Severity of acid regurgitation (past week)	0.75	1.0	0-3
Frequency awakened with heartburn or indigestion*	2.04	1.1	0-4

* Question included as part of the AWAKE Scale derived from the SHHS Sleep Habits Questionnaire, see text for additional explanation

past week (yes/no), how many times they had the symptom during the past week (frequency) and how bothersome (severity) the symptom was during the past week (i.e., 0 = not at all; 1 = somewhat; 2 = quite a bit; 3 = very much).

Three variables were created using this questionnaire. First, the frequency of GERD symptoms was calculated by summing the 15-item responses for "How many times did you have symptoms in the past week?" Second, the severity of GERD symptoms was calculated by summing and averaging the 15-item responses for "How much did the symptom bother you in the past week?" Both of these variables were significantly skewed. Therefore, a log transformation was performed to produce a normal distribution. Third, a GERD symptom index was created by multiplying the frequency and severity (both log transformed) variables.

THE SLEEP QUALITY QUESTIONNAIRE

This questionnaire was developed to assess sleep quality. The questionnaire pertains to the previous night's sleep. The questionnaire determines sleep quality by using 9 questions that assess an individual's perception of their sleep quality and behaviors as they are related to quality of sleep. The questionnaire includes items such as "how many times did you awaken during the night?" and "was your sleep restless or restful?" (rated on Likert scales from 1 = restless and 5 = restful).

A subjective measure of overall sleep quality was calculated by using the responses from 5 items that were measured on a 5-point Likert scale, summing them and obtaining the average. In the following analyses, overall sleep quality is investigated in relation to other variables, and each item was also included separately in the analysis. Other variables assessed were the number of hours spent in bed, the number of hours slept, the number of awakenings, and the number of minutes that it took to fall asleep.

The questionnaire was initially administered prior to the pH probe placement; thus responses reflected the subject's sleep quality the night before pH monitoring. After the probe was removed (the next morning), the subject again completed the questionnaire, but this time the responses reflected their sleep quality during the night of the 24-hour pH monitoring.

THE SLEEP HABITS QUESTIONNAIRE

This questionnaire was developed for use in the multisite National Heart, Lung, and Blood Institute Sleep Heart Health Study (SHHS) and one of its applications was to assess how individuals perceive their sleep on a regular basis. The Sleep Habits Questionnaire includes self-reported measures of sleep quality, arous-

als, snoring and daytime somnolence, from which we constructed 4 composite variables: the disorders of initiating and maintaining sleep (DIMS) scale, the excessive daytime sleepiness scale (EDSS), the Epworth Sleepiness Scale (ESS) and a scale related to how often a person wakes up during the night with different symptoms (AWAKE). DIMS assesses the frequency of the following: having trouble falling asleep, waking up during the night and having difficulty getting back to sleep and waking up too early in the morning and being unable to get back to sleep (0 = never, 1 = once a month or less, 2 = 2-4 times per month, 3 = 5-15 times per month and 4 = 16-30 times per month). The EDSS examines the frequency (i.e. 0 = never, 1 = once a month or less, 2 = 2-4 times/month, 3 = 5-15 times/month, 4 = 16-30 times/month) of the following symptoms: (1) feel unrested during the day no matter how many hours of sleep you had and (2) feel excessively asleep during the day. The ESS is a well validated tool that examines the likelihood (i.e. 0 = no chance, 1 = slight chance, 2 = moderate chance, 3 = high chance) of dozing off in several different activities. The AWAKE measures the frequency (i.e. 0 = never, 1 = once a month, 2 = 2-4 times/month, 3 = 5-15 times/month, 4 = 16-30 times/month) that a person wakes up with the following symptoms: (1) heartburn and indigestion, (2) coughing or wheezing, (3) shortness of breath, and (4) chest pain or tightness.

The EDSS, ESS, DIMS, and AWAKE were created by summing the responses from the appropriate items. Inasmuch as this study was focused on GERD, an item from the AWAKE scale was also analyzed separately. The question read, "How often are you awakened by heartburn or indigestion?"

Polysomnography (PSG)

Fifteen subjects (11 with erosive esophagitis and 4 with NERD) were randomly selected to undergo PSG at the University of Arizona Sleep Disorders Center to assess the effect of gastroesophageal reflux on sleep efficiency and sleep architecture. All 15 subjects underwent a PSG using a computerized digital data acquisition system (Albert Grass Heritage, Grass-Telefactor Product Group, West Warwick, RI). Each study included recording of the electroencephalogram (C_3/A_2, C_4/A_1, O_1/A_1, O_2/A_2, C_3/C_z, C_z/C_4), electro-oculogram, submental electromyogram, electrocardiographic (ECG) rhythm strip, right and left tibial electromyogram, the presence of snoring by a tracheal microphone (TR21A, Grass Instruments, Quincy, MA), airflow using a nasal-oral thermistor (Protec, Woodinville, WA), and nasal pressure transducer (Protec, Woodinville, WA), thoracic and abdominal movement (Protec, Woodinville, WA), and finger pulse oximetry (Nelcor N-100, Hayward, CA).

Table 2—The 24-hour Esophageal pH Monitoring Characteristics of the Study Participants

Variable	N	Mean	SD	Range
% total time pH < 4	47	5.7	5.0	1-21.1
% upright time pH <4	47	6.1	5.1	0.2-19.2
% supine time pH <4	47	4.6	6.3	0-24.7
Total number of acid reflux events	48	103.7	88.0	10-408
Number of upright acid reflux events	48	83.9	77.9	5-364
Number of supine acid reflux events	48	20.3	24.7	0-106
Longest acid reflux event overall (in minutes)	48	12.0	14.9	0-73
Longest acid reflux event while upright (in minutes)	48	5.9	4.3	0-18
Longest acid reflux event while supine (in minutes)	48	10.0	15.6	0-73
Total number of acid reflux events > 5 minutes	48	2.2	2.8	0-12
Number of acid reflux events > 5 minutes while upright	48	1.2	1.8	0-8
Number of acid reflux events > 5 minutes while supine	48	1.0	2.0	0-12
Symptom Index	31	0.7	0.3	0-1

Sleep was scored by a registered polysomnographic technologist using standard criteria without knowledge of the results from the questionnaires. Arousals were identified using American Sleep Disorders Association criteria. Apneas were identified as the absence of airflow ≥10 s. Hypopneas were scored if there was a 50% reduction in airflow and a 4% oxygen desaturation. Obstructive apnea events required the presence of respiratory effort throughout an event. Central apneas were scored if there was no respiratory effort, and mixed apneas were identified if there was a period of central apnea followed by evidence of obstructive apnea. In the absence of esophageal pressure measurements, hypopneas were not further classified. The apnea-hypopnea index (AHI) was defined as the number of respiratory events (apneas and hypopneas) per hour of TST. At the time this study was performed, the nasal pressure transducer signal was used only as a secondary signal to confirm the presence of apneas or hypopneas.

Data obtained during the test included: time in bed (TIB = the time from "lights off" to "final awakening"), total sleep time (TST = total amount of recorded sleep), wakefulness after sleep onset (percent of sleep period time spent awake after initial sleep onset), the percent time spent in each of 4 sleeping positions (prone, supine, left and right lateral decubitus), number of minutes spent in stage REM sleep, number of arousals associated with snoring, the snore arousal index (number of snore arousals/TST), number of arousals associated with leg movements, the leg movement arousal index (number of leg movement arousals/TST), number of spontaneous arousals and the spontaneous arousal index (number of spontaneous arousals/TST). Sleep efficiency was calculated as TST divided by TIB.

As described previously, subjects undergoing PSG had simultaneous esophageal pH monitoring. Each subject wore a pH recorder that enabled transmission of real time recorded pH measurements onto the same screen where polysomnographic and autonomic information were recorded, allowing simultaneous display and documentation of polysomnographic, autonomic, and pH data.

An experienced technician reviewed each of the 15 PSG files for episodes of acid reflux events. The duration (in minutes) of the acid reflux event was recorded, as well as the number and type of arousals (i.e., spontaneous, snore, leg movement and apnea/hypopnea-related arousals) and the stage of sleep for each epoch during the pH drop. For each period where the pH dropped below 4, a similar period during the same stage of sleep was randomly chosen in the PSG record where there was no evidence for a pH drop below 4.

Data Analyses

Data were compiled using Excel software (Microsoft, Redmond, WA). Data were then transferred to SPSS (SPSS Inc, Chicago, IL). All variables used in the analyses were checked for skewness, and if a variable was significantly skewed, that variable was log transformed so that the variable would resemble a normal distribution. Descriptive statistics were calculated and results are presented as mean ± SD. For some data, the median is provided as well. Additional analyses were conducted as follows.

First, associations between GERD symptoms and subjective sleep habits was investigated by calculating Pearson correlation coefficients using the frequency and severity variable from the GSAS questionnaire, as well as a calculated symptom index from the 24-hour pH study, and the EDSS, ESS, DIMS, and AWAKE variables from the Sleep Habits Questionnaire. Student's t-tests were used to investigate differences in sleep habits and sleep quality between the erosive esophagitis and NERD groups. Second, to determine the potential impact of poor sleep quality on GERD symptoms and severity of gastroesophageal reflux, correlations were calculated between responses to the Sleep Quality Questionnaire before pH monitoring and results from pH monitoring. Third, to assess the association between severity and frequency of reflux events and sleep quality, correlations were computed be-

Table 3—Sleep Quality and Polysomnography Data in Subjects Undergoing pH Monitoring (N=15)

Variable	Mean	SD	Range
Sleep quality pre-pH test	15.3	3.9	6-21
Sleep quality post-pH test	14.5	4.3	5-22
Periodic leg movement arousal index	3.8	5.1	0-15.4
Apnea hypopnea index	3.9	4.9	0-18.5
Respiratory arousal index	3.1	3.5	0-11.8
Snore arousal index	2.9	4.9	0-17.7
Spontaneous arousal index	14.3	8.8	5.3-38.8
Apnea arousal index	3.9	4.9	0-18.5
Total arousal index	24.0	11.7	7.9-45.1
Sleep efficiency index	81.5	13.5	50.2-94.8
Number of minutes in REM sleep	78.1	36.9	17-140

tween the results of pH monitoring and responses from the Sleep Quality Questionnaire on the morning after the pH monitoring. Finally, the polysomnography data gathered from 15 subjects who underwent this procedure were analyzed in relation to changes in pH during the night with Student's paired t-tests.

RESULTS

Forty-eight (33 males/15 females) subjects ranging in age from 20-82 years (mean ± SD age: 48.8 ± 17.1) were prospectively recruited into the study. Of those, 73% were Caucasians, 19% Hispanic, 4% African American, and 4% others. A summary of subjects' demographics, frequency and severity of heartburn and acid regurgitation (GSAS) is listed in Table 1.

The results of the upper endoscopy revealed that 18 (37.5%) subjects (12 males/6 females) had no erosions and were classified as NERD. The remaining 30 subjects (21 males/9 females) had evidence of erosive esophagitis on upper endoscopy, and of those 8 had Grade A, 10 Grade B, 7 Grade C, and 1 Grade D (Los Angeles classification). Four of the subjects (8.33%) were found to have Barrett's esophagus on endoscopy. Subjects with erosive esophagitis did not differ in their reports of frequency or severity of GERD symptoms from those with NERD.

The results of the 24-hour esophageal pH monitoring for all subjects are presented in Table 2. Overall, the mean percentage of total time pH <4 was 5.7 ± 5.0 (median 4.5). Percent upright time pH <4 was 6.1 ± 5.1 (median 6.0) and percent supine time pH <4 was 4.6 ± 4.3 (median 3.0). Seventy-one percent of the subjects had an abnormal percentage total time pH <4, 50% had an abnormal percentage upright time pH <4, and 62.5% had an abnormal percentage of supine time pH <4.

Associations Between Symptoms of Disturbed Sleep and GERD

Symptoms of disturbed sleep as assessed by the SHHS Sleep Habits Questionnaire were correlated with the presence of GERD as ascertained by the GSAS. We observed a positive correlation between the DIMS scale and the GERD symptom index (r = 0.33, p <0.05). In addition, those who reported a greater number of awakenings during the night as represented by the AWAKE scale reported a greater frequency of GERD symptoms (r = 0.35, p <0.05), a higher severity of GERD symptoms, (r = 0.40, p <0.01), and a higher GERD symptom index (r = 0.42, p <0.01). However, there were no associations between sleepiness assessed by either the EDSS or the ESS scales, and any of the indices of GERD.

We observed that there was a tendency for those subjects with erosive esophagitis to report that they woke up with heartburn more frequently than those with NERD (2.27 ± 1.08 vs. 1.67 ± 1.08, p = 0.069). However, no differences in the DIMS, EDSS, ESS, and AWAKE scales were observed between the erosive esophagitis and NERD groups.

pH Monitoring and Sleep Quality on the Preceding Night

To assess the potential impact of sleep quality on severity of gastroesophageal reflux, we performed correlations between the Sleep Quality Questionnaire obtained on the night prior to pH monitoring, and pH monitoring results and GERD symptoms the next day. We observed that poorer sleep quality overall was related to longer acid reflux events throughout the 24 hours (r

= -0.34, p <0.05) and specifically while supine (r = -0.37, p < 0.01). When individual items from the Sleep Quality Questionnaire were investigated, more perceived awakenings during the night were associated with a greater number of acid reflux events that were longer than 5 minutes in the supine position (r = 0.31, p <0.05), and the duration of the longest acid reflux event while supine (r = 0.28, p = 0.05).

Significant associations were found such that the people who reported they spent more hours in bed the night prior to the pH test, also tended to be poorer at perceiving actual acid reflux events the day of the pH test than people who spent less time in bed (r = -0.38, p <0.05). Additionally, a longer perceived sleep latency was associated with a poorer ability to perceive actual acid reflux events during the pH test (r = -0.49, p <0.01).

Sleep Quality During pH Monitoring

We observed significant correlations between acid reflux events and overall sleep quality during the night of the pH monitoring. A higher percent time spent with pH <4 while supine was related to poorer overall quality of sleep, as assessed by the Sleep Quality Questionnaire obtained on the night after pH monitoring (r = -0.432, p <0.002). The duration of the longest acid reflux in minutes both during the entire night as well as supine was associated with poorer overall reported sleep quality (Entire Night: r = -0.38, p <0.01, Supine: r=-37, p<0.02). The number of acid reflux events while supine was associated with a greater number of perceived awakenings (r = 0.431, p <0.01).

The Effect of GERD on Sleep Architecture

Fifteen subjects (8 males and 7 females; 11 with erosive esophagitis and 4 with NERD) underwent a PSG. Table 3 summarizes the data obtained during the PSG. In general, these subjects had slightly reduced sleep efficiency and did not have sleep disordered breathing. However, 4 did have an apnea-hypopnea index ≥5. Of the 15 subjects, 11 (8 with erosive esophagitis, 3 with NERD) experienced acid reflux events during the PSG. A total of 39 acid reflux events occurred among the 11 subjects. Twenty-one of the acid reflux events (53.8%) occurred during sleep.

Descriptive Pattern of Typical Drops in pH during Sleep

Although the sample size of 11 subjects (10 of whom experienced acid reflux events during sleep) is small, an interesting pattern emerged among the 21 acid reflux events. Ten of the 11 subjects experienced at least 1 acid reflux event when they were in stage 2 sleep. Additionally, 13 (62%) of the documented acid reflux events during sleep were associated with a similar physiological pattern: subjects had an acid reflux event and then awoke for an epoch (30 seconds) (Figure 2). In 3, (14.3%) of the pH drops, the subject was in REM sleep, had an epoch of wakening with subsequent acid reflux event. In another 3 of the pH drops, the subject was in REM sleep and then moved to stage 2 and had an acid reflux event. In one case, the subject was in REM sleep and had an acid reflux event while remaining in REM sleep without an arousal. Finally, one acid reflux event occurred in stage 2 sleep and the subject remained asleep without an arousal (Figure 3). Thus, in this study, we found that 19 out of 21 (90%) acid reflux events were associated with a disruption of sleep.
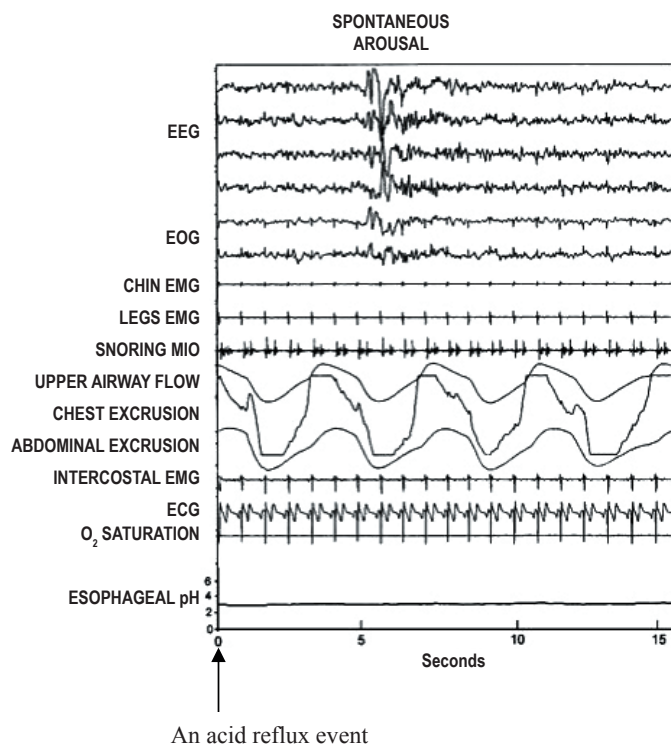
SPONTANEOUS
AROUSAL

An acid reflux event

Figure 2—A polysomnographic recording of a patient in stage 2 sleep, who experienced a spontaneous arousal associated with an acid reflux event (pH <4).

AROUSAL DIFFERENCES BETWEEN pH DROP PERIODS AND COMPARISON PERIODS

Arousals were calculated for each pH drop and comparison period where a subject was sleeping. We observed that there were more spontaneous arousals (i.e., arousals that cannot be accounted for by apneic events, leg movements, or snore arousals) during pH drops (2.85±2.72/min) than during comparison periods (1.05±2.31/min, p <0.001). However, there were no significant differences in snore arousals, hypopneas, or leg movements between periods of pH drops and comparison periods. It did not appear that the presence of arousals was associated with more rapid normalization of esophageal pH.

DISCUSSION

In this study, we found significant associations between subjectively disturbed sleep and symptoms of GERD. Sleep quality on the night before pH monitoring was related to several indices suggesting increase in reflux severity; conversely several indices of reflux severity were correlated with sleep quality assessed on the morning after the pH study. These findings suggest significant interaction between sleep quality and GERD. Our study showed that greater severity of GERD symptoms and a higher symptom index were associated with increased reports of difficulties in initiating and maintaining sleep. Furthermore, there was a tendency for subjects who reported greater nighttime awakenings to report a greater frequency and severity of GERD symptoms and a higher symptom index. Our data are consistent with previous reports demonstrating that quality of sleep correlates with severity of perceived GERD-related symptoms. By using a Gallup Poll survey, Shaker et al. demonstrated that the frequency of sleep difficulties became greater as the weekly frequency of heartburn increased. Additionally, these authors found that over two-thirds of those
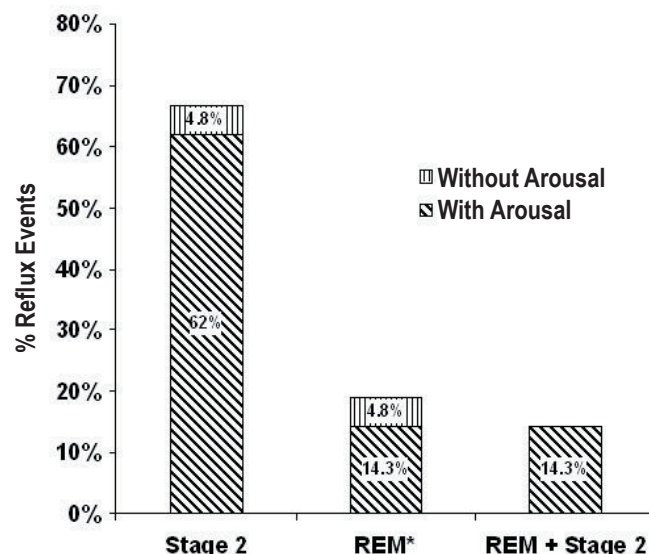

Figure 2—Distribution of acid-reflux events according to stage of sleep. Of the events that were associated with arousals (double cross-hatched), 66.8% occurred in stage 2 sleep, 14.3% occurred in REM sleep, and in an additional 14.3 percent, the event started in REM sleep, but there followed a shift to stage 2 sleep with a subsequent arousal (p <0.01). A very small number of events occurring in stage 2 and REM sleep were not associated with arousal (vertical hatched).

who experienced heartburn ≥3 times per week reported being awake or being awakened during the night because of heartburn.

To our knowledge, this study is the first to compare reports of sleep quality between individuals with NERD and those with erosive esophagitis. We observed a trend for persons with erosive esophagitis to report more awakenings during sleep because of heartburn than those with NERD. Thus, although our data did not quite achieve statistical significance (p = 0.069), they nonetheless are consistent with a previous report demonstrating that persons with erosive esophagitis experience more nocturnal esophageal acid exposure than those with NERD. This physiological phenomenon appears to be associated with increased number of awakenings during sleep of persons with erosive esophagitis as compared to those with NERD. However, in the current study, reports of sleep quality were similar between the 2 GERD groups. The discrepancy between increased awakenings during sleep and reported quality of sleep in erosive esophagitis subjects versus NERD, suggests that in those with NERD other factors, such as psychological comorbidity and stress, may affect subjective reports of sleep quality. These potential contributing factors are likely to play an important role in the largest subgroup of individuals with NERD, those with functional heartburn.

We observed that quality of sleep on the night before pH monitoring correlated with longer acid reflux events. In addition, more perceived awakenings were associated with a greater number and longer duration of reflux events, particularly in the supine position. Thus, although the associations are modest, this is the first study to suggest an effect of poor sleep quality on altering acid reflux characteristics the following day. Although never assessed in GERD, poorer than average sleep on one night has been shown to be associated with higher than average gastrointestinal symptoms the following day in persons with functional bowel disorders. The mechanism by which sleep may affect esophageal acid exposure the following day is unclear. However, it is possible that poor

quality of sleep is associated with reflux-promoting activities (for example, greater food consumption). In support of this hypothesis is recent evidence demonstrating that sleep deprivation leads to increased hunger and appetite. Alternatively, sleep disruption could modify brain-gut interactions leading to retardation in esophageal acid clearance.

In this study, acid exposure during the supine position and longer durations of individual acid reflux events were modestly associated with reduced sleep quality. Supine acid exposure, which occurs primarily during sleep, has been repeatedly shown to be associated with GERD complications, extra-esophageal manifestations of GERD and sleep disturbances. In addition, in a recent study by Johnson and colleagues, individuals with GERD-related sleep disturbances and nocturnal heartburn were treated with a proton pump inhibitor, and had a significant improvement in both their sleep disturbances and GERD. Thus, it is not surprising that we found more severe esophageal acid exposure to be detrimental for our subjects' perceived sleep quality.

Analyses of our PSG data revealed that most acid reflux events occurred during stage 2 sleep. In 90% of the subjects, acid reflux events were associated with short arousals (about 30 seconds), for which all subjects were amnestic. Our study also demonstrated that a higher arousal index was significantly associated with poorer quality of sleep. These results suggest that there are at least 2 mechanisms by which gastroesophageal reflux may cause poor quality of sleep. First, sleep disruption may occur through short, amnestic, arousals during the night. These arousals might lead to increased sympathetic activation manifested by events such as increases in heart rate or blood pressure. It has been proposed that such increases in heart rate or blood pressure represent autonomic arousals and can result in a decrease in subjective sleep quality even in the absence of electroencephalographic evidence of cortical arousal. However, the frequency of acid reflux events observed in our study was low in comparison to the total arousal frequency, and may not by itself be an explanation for sleep disruption with GERD. A second mechanism may be the duration of esophageal contact time with each event. In support of this mechanism are our observations that sleep quality was associated with longer duration of acid reflux events.

We observed that most acid reflux episodes began before electroencephalographic evidence of arousal. The temporal relationship between episodes of acid reflux during sleep and arousals is unclear. In some cases, arousals can result in transient lower esophageal relaxation leading to acid reflux. However, this does not appear to be a uniform finding. In one study, respiratory events (apnea/hypopnea) preceded or occurred during an acid reflux event.[28] However, in this study we excluded patients with sleep apnea. In another study, it was suggested that arousals may precede, occur during or after an acid reflux event.[29] Different techniques to assess acid reflux during sleep my explain the discrepancy. Further studies are needed.

Changes in autonomic nervous system activity may mediate the sleep disruption observed with GERD. Several studies have shown disturbances of the parasympathetic branch of the autonomic nervous system in persons with GERD with or without erosive esophagitis. Chakraborty et al. demonstrated that autonomic dysregulation in patients with GERD was limited solely to the cardiovascular part of the parasympathetic branch of the autonomic nervous system.[30] No studies have specifically assessed the nighttime response of the autonomic nervous system to acid reflux events; nevertheless, it is plausible that diminished sleep quality in those with GERD is mediated in part by reflux induced autonomic arousals.

One of the unique aspects of our study is that we assessed sleep quality before and after esophageal pH monitoring. This allowed us in a limited fashion to assess the potential impact of poor sleep quality on acid reflux events, and vice versa. Although certainly preliminary, our data suggest that not only can gastroesophageal reflux adversely affect sleep quality, but that poor quality of sleep may in turn exacerbate gastroesophageal reflux the following day leading to further sleep deprivation. This reciprocal augmentative relationship, between quality of sleep and gastroesophageal reflux may lead to symptomatic sleep disturbances and reports of poor quality of life. Anti-reflux medications appear to break this vicious cycle and improve reports of sleep quality.

There are several limitations to this study. First, the study design required sleep assessment during 24-hour esophageal pH monitoring, and thus some may argue that the test itself may have affected sleep quality. However, in a study by Fass et al. evaluating the impact of pH testing on reflux provoking activities, the authors found no difference between the frequency of sleep abnormalities in the presence or absence of pH testing.[31] Second, a relatively small number of subjects had PSGs; even though these subjects were randomly selected, our conclusions with respect to changes in sleep architecture may have been influenced by inadvertent selection bias. Third, although we utilized a nasal pressure transducer in our PSG montage, it was not used as the primary sensor for identifying apneas and hypopneas. We do not believe this affects our results because sensitivity analyses (data not presented) indicated that our observations remained after removing the few subjects with an elevated apnea hypopnea index. Nevertheless, we cannot exclude a possible effect of unidentified respiratory effort related arousals. Fourth, we acknowledge that the strength of the associations we observed were modest and thus indicative of the presence of other factors influencing these relationships. Validation of our hypothesis that poor sleep quality leads to more gastroesophageal reflux will require studies of longer duration with a greater number of participants. Our study is a first step in addressing this question.

In conclusion, this is the first study to evaluate the relationships between GERD on quality of sleep, and quality of sleep on GERD. Both esophageal acid reflux profile and subjects' perceptual responses were associated with quality of sleep. In turn, quality of sleep at night was related to the esophageal acid reflux profile the following day. These observations will require confirmation in future studies.

ABBREVIATIONS

GERD: gastroesophageal reflux disease
NERD: non-erosive reflux disease
WASO: wake time after sleep onset
REM: rapid eye movement
EDSS: excessive daytime sleepiness scale
ESS: Epworth Sleepiness Scale
TST: total sleep time
DIMS: Disorders of initiating and maintaining sleep

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Appendix—Sleep Quality Questionnaire

1. What time did you go to sleep last night? _____ am/pm

2. What time did you wake up today? _____ am/pm

3. How long did you spend in bed last night? _____hrs._____ min.

4. How long did you sleep last night _____hrs._____ min.

5. How many times did you awaken during the night? _____

6. Did you have difficulty falling asleep last night ___ Yes___ No

7. How many minutes did it take for you fall asleep at bedtime last night? _____ min.

8. Please rate the quality of your sleep last night by circling a number from 1 to 5 on each of the scales below.

A.   Light   Deep
     1   2   3   4   5
B.   Short   Long
     1   2   3   4   5
C.   Restless   Restful
     1   2   3   4   5
D.   Poor   Excellent
     1   2   3   4   5

9. How rested did you feel this morning after awakening from sleep?

     Not at all   Well rested
     1   2   3   4   5

Questionnaire adapted from the Sleep Heart Health Study Morning survey and Armitage *et al. Depression and Anxiety* 1997;5:97-102.